

# PATENT SPECIFICATION

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## (54) 4-OXO-4H-BENZOPYRYAN DERIVATIVES AND PROCESS FOR THEIR PREPARATION

(71) We, PFIZER LIMITED, a British Company of Ramsgate Road, Sandwich, Kent, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

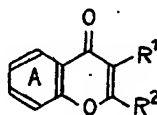
This invention relates to 4-oxo-4H-benzopyran derivatives and is particularly concerned with a process for the preparation of 3-substituted 4-oxo-4H-benzopyrans from hydroxy-phenyl ketones by reacting them with a formylating reagent of the Vilsmeier type in the presence of boron-trifluoride etherate, and with novel 3-substituted 4-oxo-4H-benzopyrans.

Many 3-substituted-4-oxo-4H-benzopyrans are known and in particular various 3-phenyl derivatives (isoflavones) have been proposed in the past as feed additives capable of promoting the growth or improving feed conversion efficiency in economically important animals. Other 3-substituted-4-oxo-4H-benzopyrans have been proposed as anti-allergic drugs.

Existing processes for the preparation of such compounds are frequently multistage and of limited utility; as for example the synthesis of isoflavones described by Baker and Ollis (Nature, 1952, 169, 706) and by Baker, Chadderton, Harborne and Ollis (J. Chem. Soc., 1953, 1852). The use of the Vilsmeier reaction has been described by Kagal, Nair and Venkataraman (Tet. Letters, 1962, 593) but this process is not of general utility. For example it fails in the case of polyhydroxy-phenyl ketones. In addition when isoflavones are prepared by this process the major product is commonly a compound in which the aromatic ring is formylated. Ring formylated by-products are in any case often present in the product obtained by this process.

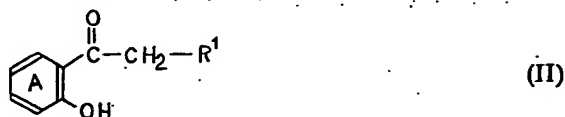
We have now discovered a general process for the preparation of 3-substituted-4-oxo-4H-benzopyrans from 2-hydroxy-phenyl ketones in which the use of a formylating reagent of the Vilsmeier type in the presence of boron-trifluoride etherate enables the preparation of such compounds in a single stage without the formation of ring formylated by-products.

Thus, the invention provides a process for the preparation of compounds of the general formula:—



(I)

in which R<sup>1</sup> represents an aryl group, a heteroaryl group, a cycloalkyl group, an aralkyl group, a lower alkoxy group, an aryloxy group, or an aryl-sulphonyl group; R<sup>2</sup> represents a hydrogen atom or a lower alkyl group; and the ring A may optionally be substituted with one or more halogen atoms or hydroxyl, lower alkyl or lower alkoxy groups; which comprises reacting a 2-hydroxy-phenyl ketone of the formula:—



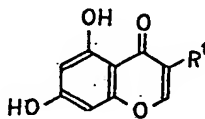
(wherein  $R^1$  and the ring A are as previously defined) with at least one molar proportion of an N,N-dialkyl or N-alkyl-N-aryl-amide of formic or a  $C_2$  to  $C_3$  alkanolic acid and a strong acid chloride, as herein defined, in excess amide reagent or in a reaction inert organic solvent, in the presence of boron-trifluoride etherate, followed in the case where ring A is substituted with one or more hydroxyl groups and an amide of a  $C_2$  to  $C_3$  alkanolic acid is used, by hydrolysis of the resulting O-acylated product.

In the above and elsewhere in this specification the term lower applied to an alkyl or alkoxy group indicates that such a group contains up to 4 carbon atoms and may be straight or branched chain. Halogen means fluorine, chlorine, bromine or iodine. By "aryl" is meant an aromatic hydrocarbon group, e.g. a phenyl or naphthyl group, which may or may not be substituted; by "heteroaryl" is meant an aromatic heterocyclic group, e.g. a pyridyl group; by "aralkyl" is meant an aryl-substituted lower alkyl group.

In the reaction, acylation of the activated methylene group is accompanied by concomitant ring closure to yield, after suitable work-up, the benzopyran compounds of formula (I).

The strong acid chloride is defined as phosphorus oxychloride, thionyl chloride, phosgene, oxaloyl chloride, methane-sulphonyl chloride, benzene-sulphonyl chloride or para-toluene-sulphonyl chloride. Particularly preferred reagents for effecting the cyclisation are N,N-dimethylformamide or N,N-dimethylacetamide with methane-sulphonyl chloride in the presence of boron-trifluoride etherate. The reaction is preferably carried out with the 2-hydroxyphenyl ketone dissolved in a solvent consisting of excess dry dimethylformamide or dimethylacetamide (depending on whether  $R^2$  is to be hydrogen or methyl), and to this solution may be added the boron-trifluoride etherate, preferably in an amount of from 3 to 6 equivalents, based on amount of ketone used. A solution containing methane-sulphonyl chloride dissolved in excess dry dimethylformamide or dimethylacetamide is then added, preferably in excess (allowing 1 equivalent excess of methane-sulphonyl chloride for each hydroxyl group present in the ketone used), and the mixture is then heated until the reaction is complete. We have found that when the reaction is performed at  $80^\circ\text{C}$  e.g., by heating on a steam bath, the reaction is substantially complete within 2 hours. The product is then conveniently isolated from the reaction mixture by adding water to the cooled reaction mixture or by pouring into a large volume of cold water. The solid product is recovered by filtration and further purification, if required, can be effected by recrystallisation. In the case where dimethylacetamide is used as the solvent to give the 2-methyl compounds of formula (I) where  $R^2=\text{CH}_3$ , the product is initially isolated with any hydroxy groups present as substituents in ring A acetylated. The free hydroxy groups may be readily regenerated by mild acid hydrolysis.

We have found the present process to be useful for the preparation of compounds of the formula I where the ring A is substituted with a hydroxyl group in the 5 and/or 7 positions and to be particularly advantageous for the synthesis of 5,7-dihydroxy-isoflavones of the formula:



where  $R^1$  is a phenyl or substituted phenyl group, and for the synthesis of novel 3-substituted 4-oxo-4H-benzopyrans of formula (I) where  $R^2$  is hydrogen and  $R^1$  is as previously defined other than a phenyl, substituted phenyl or heteroaryl group.

The starting materials of formula (II) are generally known compounds or are readily accessible by conventional methods. For example, they may be obtained by the Houben-Hoesch reaction of a hydroxy-phenol with a nitrile of the formula  $R^1\text{CH}_2\text{CN}$  or by a Friedel-Crafts reaction between a phenol and an acid of the formula  $R^1\text{CH}_2\text{COOH}$  or an ester, acid chloride or anhydride thereof.

The present invention also provides certain novels 5,7-dihydroxyisoflavones of formula (III) above wherein  $R^1$  is a 4-isopropyl-phenyl, 4-bromo-phenyl, *p*-tolyl, 3-chloro-phenyl, *p*-biphenyl or 4-methane-sulphonyloxy-phenyl group.

Also are provided novel 3-substituted-4-oxo-4H-benzopyrans of formula (I) in which  $R^2$  is a hydrogen atom and  $R^1$  is as previously defined other than a phenyl, substituted phenyl or heteroaryl group including the following:

5,7-dihydroxy-3-benzyl-4-oxo-4H-benzopyran,  
5,7-dihydroxy-3-phenylsulphonyl-4-oxo-4H-benzopyran,  
5,7-dihydroxy-3-(4-methoxyphenoxy)-4-oxo-4H-benzopyran,  
5,7-dihydroxy-3-methoxy-4-oxo-4H-benzopyran,  
7-hydroxy-3-(naphth-1-yl)-4-oxo-4H-benzopyran,  
7-hydroxy-3-(naphth-2-yl)-4-oxo-4H-benzopyran,  
5-hydroxy-3-(4-hydroxy-benzyl)-7-methyl-4-oxo-4H-benzopyran and compounds in which  $R^1$  is a cycloalkyl group containing 5 or 6 carbon atoms, e.g.:  
6-hydroxy-3-cyclohexyl-4-oxo-4H-benzopyran,  
7-hydroxy-3-cyclopentyl-4-oxo-4H-benzopyran,  
6-hydroxy-3-cyclopentyl-4-oxo-4H-benzopyran, and  
6-chloro-7-hydroxy-3-cyclohexyl-4-oxo-4H-benzopyran.

The novel compounds of the invention are useful for promoting growth or improving feed conversion efficiency in animals. One particularly preferred novel compound of the invention is 7-hydroxy-3-(naphth-2-yl)-4-oxo-4H-benzopyran. The compound of formula (I) may be administered in the animal feed or drink, or it may be administered to the animal orally in other ways, or parenterally or as an implant. When it is administered in the feed it may be added thereto in amounts of from 1 g to 100 g per tonne of feed. For convenience of distribution it will, however, normally be marketed in the form of a concentrate in which the compound is mixed with an inert diluent such as limestone or oystershell powder or with other feed components, e.g. at levels of from 1 to 100 g per kg of concentrate.

Thus, also according to the invention there are provided feed compositions for animals which comprise a nutritionally balanced feed composition in which is incorporated a growth promoting or feed conversion efficiency improving amount of a novel compound of the formulae (I) or (III).

Also according to the invention, a composition suitable for adding to animal feeds comprises a novel compound of the formulae (I) or (III) together with a solid diluent compatible with animal feeds.

For oral or parenteral administration, or for administration as an implant, the compound of formula (I) may be used as such, but will more generally be used in admixture with a pharmaceutical carrier selected with regard to the intended mode of administration and according to veterinary pharmaceutical practice.

For example, it may be administered orally as a bolus or capsule containing excipients such as starch or lactose, or as a drench consisting of a solution or suspension of the compound in an aqueous vehicle containing flavouring matter if necessary. For parenteral administration, e.g. by depot injection, it may be administered as a suspension in a pharmaceutically-acceptable oil, e.g. arachis oil, suitable for dosages being in the range from 0.1 to 100 mg per animal. For administration as an implant, it may be formulated as a pellet with an excipient such as maize starch, lactose or glycine to release the active ingredient at an appropriate rate. Such pellets for implants may suitably contain from 50 to 80% of the active ingredient by weight.

The invention will now be more particularly described by reference to the following Examples which illustrate the novel process of the invention and describe the preparation of the novel compounds of formulae I and III.

#### EXAMPLE 1.

2,4,6-Trihydroxy-phenyl 4-methyl-benzyl-ketone (13.0 g) was dissolved in dry dimethylformamide (100 ml) and boron-trifluoride etherate (42.4 g) was added cautiously, with stirring. A solution of methane-sulphonyl chloride (17.3 g) dissolved in dry dimethylformamide (100 ml) was added and the mixture was heated for 2 hours on the steam bath. The reaction mixture was cooled, poured slowly into cold water (1 l) with stirring and allowed to stand overnight. The solid product was collected by filtration and recrystallised from a mixture of ethanol and water to yield 5,7-dihydroxy-3-*p*-tolyl-4-oxo-4H-benzopyran (11.5 g, 85% yield), m.p. 215–217°C. (Found: C, 71.3; H, 4.6.  $C_{16}H_{12}O_4$  requires C, 71.6; H, 4.5%)

## EXAMPLES 2 to 16.

The following 3-substituted-5,7-dihydroxy-4-oxo-4H-benzopyrans were prepared starting from the appropriate 2,4,6-trihydroxy-phenyl ketone by the same procedure as described in Example 1. Table I shows the 3-substituent ( $R^1$ ) together with the melting point and analytical data for the compounds. In all cases the compounds were shown to be single component by TLC and the structures were confirmed by NMR and IR spectroscopy.

TABLE I

5,7-Dihydroxy-4-oxo-4H-benzopyrans (formula III)

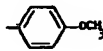


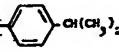




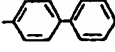





Example	R <sup>1</sup>	m.p. °C	Analysis % (Theoretical in brackets)
2		211–213° (lit. <sup>1</sup> 211–212°)	
3		>330° <sup>6</sup>	C, 52.0; H, 2.7; N, 3.9 (C, 52.0; H, 2.7; N, 3.8) <sup>6</sup>
4		225–226° (lit. <sup>2</sup> 224–225°)	
5		136–137°	C, 72.7; H, 5.4 (C, 73.0; H, 5.4)
6		250–252°	C, 53.7; H, 2.8 (C, 54.1; H, 2.7)
7		230°	C, 62.25; H, 3.1 (C, 62.4; H, 3.1)
8		301–303° lit. <sup>3</sup> 294–295°)	C, 59.5; H, 3.00; N, 5.1 (C, 59.3; H, 3.1; N, 4.6) <sup>4</sup>
9		195–196° (lit. <sup>3</sup> 206–208°)	
10		245–247°	C, 74.7; H, 4.4 (C, 74.3; H, 4.45) <sup>4</sup>
11		236° (lit. <sup>2</sup> 236–237°)	
12		178°	C, 52.6; H, 3.55 (C, 52.2; H, 3.7) <sup>5</sup>
13		233–235°	C, 56.5; H, 3.4 (C, 56.6; H, 3.2)

TABLE I (cont.)

5,7-Dihydroxy-4-oxo-4H-benzopyrans (formula III)

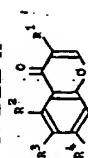
Example	R <sup>1</sup>	m.p. °C	Analysis % (Theoretical in brackets)
14		177-178°	C, 70.7; H, 4.5 (C, 70.5; H, 4.6) <sup>4</sup>
15	-OCH <sub>3</sub>	229-231°	C, 57.2; H, 3.8 (C, 57.7; H, 3.9)
16		180°	C, 62.36; H, 4.10 (C, 62.16; H, 4.23) <sup>5</sup>

<sup>1</sup> Biochanin A<sup>3</sup>.<sup>2</sup> J. Med. Chem., 1967, 10, 154.<sup>3</sup> J. Chem. Soc., 1953, 1852<sup>4</sup> Calculated for ¼ H<sub>2</sub>O.<sup>5</sup> Calculated for ½ H<sub>2</sub>O.<sup>6</sup> Trifluoroacetate salt

## EXAMPLES 17 to 30.

The following 3-substituted-4-oxo-4H-benzopyrans were prepared from the appropriate di-hydroxy-phenyl ketone by the same procedure as described in Example 1. Table 2 shows the structures of compounds prepared together with their melting points and analytical data. The compounds were shown to be single component by T.L.C. and the structures were confirmed by NMR and IR spectroscopy.

TABLE II



Example	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	m.p. °C	Analysis % (Theoretical in brackets)
17		H	OH	H	202°	C, 73.55; H, 6.7 (C, 73.75; H, 6.6)
18		H	H	OH	203°	C, 73.2; H, 6.0 (C, 73.0; H, 6.1)
19		H	OH	H	219°	C, 73.1; H, 5.9 (C, 73.0; H, 6.1)
20		H	Cl	OH	252°	C, 63.6; H, 5.45 (C, 63.6; H, 5.5)
21		H	H	OH	208° (lit. <sup>1</sup> 213°)	
22		H	H	OH	258-259° (lit. <sup>2</sup> 257-258°)	

TABLE II (Continued)









Example	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	m.p. °C	Analysis % (Theoretical in brackets)
23		H	H	OH	305°	C, 78.7; H, 4.2 (C, 79.1; H, 4.2)
24		H	H	OH	278°	C, 79.2; H, 4.3 (C, 79.1; H, 4.2)
25		CH <sub>3</sub>	H	CH <sub>3</sub>	150-151°	C, 76.5; H, 5.7 (C, 77.1; H, 5.75)
26		OH	H	CH <sub>3</sub>	188-190°	C, 71.55; H, 4.5 (C, 71.6; H, 4.5)
27		CH <sub>3</sub>	H	OH	>320°	C, 70.1; H, 4.5 (C, 70.5; H, 4.6) <sup>3</sup>
28		OH	H	CH <sub>3</sub>	148-149°	C, 65.7; H, 3.9 (C, 66.0; H, 4.0) <sup>3</sup>



TABLE II (Continued)

Example	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	m.p. °C	Analysis % (Theoretical in brackets)
29		OH	H	CH <sub>3</sub>	228°	C, 72.1; H, 5.2 (C, 72.3; H, 5.0)
30		OCH <sub>3</sub>	H	OCH <sub>3</sub>	135-136°	C, 64.3; H, 4.1 (C, 64.6; H, 4.1)

<sup>1</sup> J. Chem. Soc., 1934, 1121.<sup>2</sup> J. Endocrin., 1962, 24, 341.<sup>3</sup> Calculated for ¼ H<sub>2</sub>O.

## EXAMPLE 31.

2,4,6-Trihydroxy-phenyl 4-fluoro-benzyl-ketone (1.31 g, 5 mmole) was dissolved in dimethylacetamide (5.0 ml) and boron-trifluoride etherate (2.1 g, 15 mmole) was added cautiously. This solution was then added to a solution of methane-sulphonyl chloride (1.71 g, 15 mmole) in dimethylacetamide (5 ml) and the resulting mixture was heated on the steam bath for 75 minutes. The reaction mixture was poured into cold water (75 ml) and the crystalline diacetate was collected by filtration. The product was hydrolysed by heating in 50% methanolic hydrochloric acid (20 ml, 5N) at reflux for 1 hour, the solution was poured into excess cold water and the crystalline precipitate was collected and dried to give 5,7-dihydroxy-3-p-fluoro-phenyl-2-methyl-4-oxo-4H-benzopyran, m.p. 222-223°. NMR of the diacetate confirmed that cyclisation had taken place. The product was identical in T.L.C. with a sample prepared via the standard Allen-Robinson synthesis.

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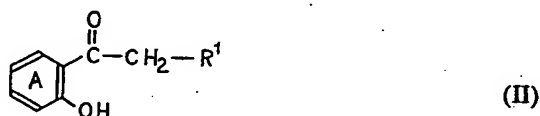
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## WHAT WE CLAIM IS:—

1. A process for the preparation of compounds of the general formula:



in which R¹ represents an aryl group, a heteroaryl group, a cycloalkyl group, an aralkyl group, a lower alkoxy group, an aryloxy group, or an aryl-sulphonyl group; R² represents a hydrogen atom or a lower alkyl group; and the ring A may optionally be substituted with one or more halogen atoms or hydroxyl, lower alkyl or lower alkoxy groups; which comprises reacting a 2-hydroxy-phenyl ketone of the formula:



(wherein R¹ and the ring A are as previously defined) with at least one molar proportion of an N,N-dialkyl or N-alkyl-N-aryl-amide of formic or a C₂ to C₃ alkanolic acid and a strong acid chloride as herein defined, in excess amide reagent or in a reaction inert organic solvent, in the presence of boron-trifluoride etherate, followed, in the case where ring A is substituted with one or more hydroxyl groups and an amide of a C₂ to C₃ alkanolic acid is used, by hydrolysis of the resulting O-acylated product.

2. A process as claimed in claim 1 when performed in excess N,N-dimethylformamide or N,N-dimethylacetamide as solvent.

3. A process as claimed in claim 1 or 2 wherein the strong acid chloride is methane-sulphonyl chloride.

4. A process for the preparation of compounds of the formula (I) as claimed in any previous claim wherein the ring A is substituted with a hydroxyl group in the 5 and/or 7 positions and R¹ and R² are as previously defined.

5. A process as claimed in claim 4 wherein the group R¹ is a phenyl or substituted phenyl group and the ring A is substituted with a hydroxyl group in the 5 and 7 positions.

6. A process as claimed in claims 1, 2 or 3 wherein R² is hydrogen and the group R¹ is other than a phenyl, substituted phenyl or heteroaryl group.

7. A process as claimed in claim 1 substantially as described in any one of the Examples.

8. Compounds of the formula:



wherein R¹ is a 4-isopropyl-phenyl, 4-bromo-phenyl, p-tolyl, 3-chloro-phenyl, p-biphenyl or 4-methanesulphonyloxyphenyl group.

9. Compounds of the formula (I) in which R² is hydrogen and R¹ and ring A are as defined in claim 1 other than those in which R¹ is a phenyl, substituted phenyl or heteroaryl group.

10. A compound as claimed in claim 9 in which R¹ is a cycloalkyl group containing 5 or 6 carbon atoms.

11. 7-hydroxy-3-(naphth-2-yl)-4-oxo-4H-benzopyran.

12. A method of promoting growth or improving feed conversion efficiency in non-human animals which comprises administering an effective amount of a compound as claimed in any one of claims 8 to 11.

13. A feed composition for animals which comprises a nutritionally balanced feed composition in which is incorporated a growth promoting or feed conversion

efficiency improving amount of a compound as claimed in any one of claims 8 to 11.

14. A composition suitable for adding to animal feeds comprising a compound as claimed in any one of claims 8 to 11, together with a solid diluent compatible with animal feeds.

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Chartered Patent Agent,  
Agent for the Applicants.

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